REMARKS

I. Status of the Claims

Claims 1-14 and 16-20 are pending and stand rejected under 35 U.S.C. §103 and under the doctrine of obviousness-type double-patenting. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Applicants have provided a substantially revised claim set that almost exclusively provides clarifying amendments to the existing claims. New claims 21-26 merely set forth dependent embodiments calling out the use of phosphocholine in particular. As such, no new matter is introduced by the amendments and new claims.

II. Rejection for Alleged Obviousness-Type Double-Patenting

Claims 1-14 and 16-20 are rejected under the judicially-created doctrine of obviousness-type double-patenting over U.S. Patent 6,780,605 in view of Muzya *et al.*, optionally further in view of Baldo *et al.* Applicants traverse, but in the interest of advancing the prosecution, applicants submit a terminal disclaimer to address this rejection. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Rejections Under 35 U.S.C. §103

A. Barquinero, Muzya and Ostermann

Claims 1-13 stand rejected as obvious over Barquinero *et al.*, in view of Muzya *et al.* and Ostermann *et al.* Barquinero is cited as teaching correlation between SLE and anti-PAF levels (with SLE allegedly leading to inflammation and cardiovascular disease), Muzya is cited as teaching that antibodies binding to PAF also bind to lyso-PAF and acyl analogs of PAF, and

Ostermann is cited as teaching PAF quantification in serum and plasma as well as correlation/diagnosis with atherosclerosis. Applicants traverse.

1. Interview

Applicants wish to thank the examiner and her supervisor for the courtesy of an in-person interview, held at the Patent and Trademark Office, on November 15, 2006, including Examiner Cook, SPE Long Le, and the undersigned. During the interview, the undersigned addressed each of the references cited above and explained why the examiner had either misinterpreted the substance of the teachings of those papers, or improperly attributed motivation to make modifications to the art where none existed. While agreement was not reached, it was agreed that Barquinero did not teach correlation between anti-PAF and autoimmune disease, *e.g.*, SLE, as previously argued. It was agreed that applicants would reiterate their position with regard to all of the references and non-obviousness in a formal response to the action. ***As urged at the conclusion of the interview, applicants request that should the examiner fail to find the claims as submitted herein allowable, a telephone call to the undersigned be initiated prior to issuance of a further action.***

2. Lack of a Prima Facie Case

First, applicants would like to draw the examiner's attention to new claim 1, which now reads as follows:

> A method for diagnosing early cardiovascular disease comprising (a) contacting a sample of body fluid with phosphocholine and/or a derivative thereof, (b) assessing the presence and/or concentration of antibodies to phosphocholine and/or to said derivative in the sample by measuring antibodies bound to phosphocholine and/or derivative thereof, and (c) diagnosing early cardiovascular disease based on the presence and/or concentration of said antibodies in the sample.

Thus, the claim as written is quite straightforward – an assay for antibodies that bind to phosphocholine or a derivative thereof as a diagnostic for early cardiovascular disease (CVD).

The examiner has cited Barquinero as teaching a correlation between anti-PAF antibodies and autoimmune diseases such as SLE, with SLE having inflammatory and hence cardiovascular disease components. As applicants' representative pointed out during the interview, however, Barquinero does ***not*** teach a correlation with anti-PAF antibodies and autoimmune disease. Much to the contrary, Barquinero readily admits that "[o]nly differences between syphilis and normal blood donors were significant ($P < 0.01$)." Barquinero, Discussion, 1st para. Indeed, of some 128 SLE patients and 28 PAPS patients, only 10 and 5 patients, respectively, showed elevated anti-PAF, as opposed to 30 out of 40 syphilis patients. Barquinero, Table 1. During the interview, the examiner and her supervisor agreed that Barquinero could not provide a link between anti-PAF and early CVD.

Turning to the secondary reference, applicants submit that Muzya clearly has no relevance with respect to the present rejection as it addresses gynecologic disorders.[1] Though the examiner was citing this reference for the proposition that there might be some relationship between anti-phospholipid antibodies and anti-PAF antibodies, the fact that this paper addresses a completely different disease state strongly suggests that it cannot properly be relied upon here, even in that context.

Turning to the tertiary reference in this rejection, we are still looking for a link between anti-PAF antibodies and CVD. Ostermann cannot provide that link, however, for the simply reason that ***it never once mentions anti-PAF antibodies***. What Ostermann does appear to teach is a correlation between the activity of a PAF acetylhydrolase activity and atherosclerosis.

However, Ostermann never shows that PAF degradation correlates with a reduced level of PAF, and even more importantly, it never addresses anti-PAF antibodies (much less anti-PC antibodies) that might actually be expected to ***drop*** if indeed the PAF levels in these patients are reduced.

In sum, applicants submit that the cited reference lack at least one fundamental teaching that is a prerequisite for advancing a rejection against present claim 1, namely, that there is any link between anti-PAF or anti-PC antibodies and CVD. For this simple reason, the rejection must fall. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

B. Barquinero, Muzya, Ostermann and Baldo

Claims 14 and 16-20 stand rejected as obvious over Barquinero *et al.*, in view of Muzya *et al.* and Ostermann *et al.*, and further in view of Baldo *et al.* Each of the first three references is cited as above, whereas Baldo is cited for phospholipid analogs that are sufficient to induce anti-PAF antibodies, PAF being known to be insufficiently antigenic to produce anti-PAF antibodies in standard immunization schemes. Once again, applicants traverse.

For the reasons presented above, this rejection is flawed as well. Baldo provides no teaching that would provide the basis for linking anti-PAF antibodies or anti-PC antibodies to CVD. This alone is sufficient to overcome the rejection. However, it also is worth pointing out that the citation of Baldo is illogical in the context of an immunoassay. Taking the examiner's statements at face value, one interested in ***generating*** anti-PAF antibodies might be motivated to use various of Baldo's phospholipids due to the apparent low antigenicity of PAF. However, when the goal is to ***identify*** anti-PAF antibodies, there would be ***no*** logical reason to use

[1] Applicants are providing a certified translation of the entire Muzya *et al.* paper, as the examiner had (and apparently has) only access to a translated abstract.

something other than ***PAF itself***. PAF is not in short supply, expensive, or difficult to use. Moreover, as noted by Barquinero, there is a difference in the ability of charged phospholipids to ***cross-react*** with anti-PAF, and in their ability to ***compete*** with PAF for anti-PAF binding. Indeed, Muzya comments that "[i]n contrast to highly specific antibodies to PAF, aPC antibodies are not highly specific and reactive with other phospholipids." Muzya, 2nd para. following Table 2. This is a clear condemnation of using anything other than PAF in anti-PAF assays.

Again, applicants submit that the cited references lack the fundamental teaching that there is any link between anti-PAF or anti-PC antibodies and CVD. Moreover, there is no motivation for using things other than PAF in an assay for anti-PAF. For both of these reasons, the rejection must fall. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should there be any questions regarding this submission a telephone call to the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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